

REMARKS

Status of the Application

Claims 29-49 were pending in the application at the time the Office Action was mailed. Claims 32 and 33 were withdrawn as being directed to non-elected subject matter. Claims 29-31 and 34-49 are currently under examination on the merits. Claims 29-31 and 34-49 were rejected in the Office Action. No claims were allowed.

By this paper, claims 29-31 are amended. No claims have been added or canceled. The amendments presented herein have been made solely to expedite prosecution of the instant application to allowance and should not be construed as an indication of Applicant's agreement with or acquiescence to the Examiner's position or as surrender of any subject matter in the instant application. Accordingly, Applicant expressly maintains the right to pursue broader subject matter through subsequent amendments, continuation or divisional applications, reexamination or reissue proceedings, and all other available means. The amendments and rejections are addressed below in more detail.

Claim Rejections - 35 U.S.C. §112

Claims 29-31 and 34-49 were rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for "a method of using a composition for the preparation of a drug for...treatment of psychiatric disturbances", allegedly does not reasonably provide enablement for "preventing...the psychiatric disturbances". According to the Office Action, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicant disagrees with this rejection, but solely in order to expedite prosecution, claim 29 (from which claims 29-31 and 34-49 depend) has been amended herein to recite "for the treatment of" rather than "for the prevention and/or treatment of."

Accordingly, withdrawal of these rejections is respectfully requested.

Claim Rejections - 35 U.S.C. §103

Claims 29-31 and 34-49 were rejected under 35 U.S.C. §103(a) as being unpatentable over Nishikawa et al. (U.S. Patent No. 6,306,907) and Horrobin (U.S. Patent No. 4,977,187), and further in view of Chen (U.S. Patent No. 6,759,435). The Examiner states:

The claims differ from the cited references in claiming combination of DHA and EPA and GLA composition of Horrobin to treat schizophrenia. To employ combinations of DHA and EPA & GLA (gamma-linolenic acid: n-6 essential fatty acid) composition to treat schizophrenia would have been obvious because all the components are well known individually for treating schizophrenia. It would be expected that the combination of components would schizophrenic conditions as well. One of ordinary skill in the art would have combined the antischizophrenic agents by known methods and that in combination, each element merely would have performed the same antischizophrenic activity as it did separately.

Applicants respectfully disagree with this rejection. The combination of Nishikawa et al., Horrobin and Chen does not yield a *prima facie* case of obviousness because none of Nishikawa et al., Horrobin and Chen provide an implicit or explicit motivation to a skilled person to modify their teachings such that they result in the presently claimed invention, and because the teachings of the prior art would discourage one from attempting to treat schizophrenia as currently claimed, i.e., the prior art *teaches away* from the presently claimed invention. In addition, the results of the presently claimed invention were unexpected in view of the prior art and the conventional wisdom at the time the application was filed. Applicant's experimental results described in Example 6 of the application, and in the 1.132 Declaration filed herewith, show that the presently claimed method alleviates symptoms of Schizophrenia in mammals. These results are unexpected, since the prior art teaches away from the claimed combination of DHA and EPA, and because the prior art teaches that GLA is an essential feature of a composition for treating Schizophrenia, yet the presently claimed method that alleviates Schizophrenia symptoms in mammals involves a composition that does not include GLA.

Regarding Nishikawa et al., this reference relates to the treatment of psychosis in general and not to schizophrenia specifically, as present claim 29 does. It can be deduced from Nishikawa et al. that psychosis is distinct from schizophrenia ("psychosis is a mental disease characterized by, for example, schizophrenia" – col. 1, lines 8-9), but this concept is also clearly established in the medical literature (see e.g. the enclosed excerpts from Merck Manual Home Edition, filed with a Supplementary Information Disclosure Statement (IDS) herewith). Concerning the materials in Nishikawa et al., this reference teaches (col. 2, lines 41-46) that sardine oil is saponified to form a fatty acid, which is then subjected to alcoholysis to give an ethyl ester, which is separated and purified on molecular distillation equipment to yield ethyl

docosahexaenoate having a high purity. However, neither from this disclosure nor from any other teachings of this reference is it possible to draw any indications about the concentration of the product. It appears that the major concern of Nishikawa et al. is the purification, in that it is well known that fish oils, further to containing some dozens of heterogeneous fatty acids, are strongly contaminated by numerous foreign substances, such as degradation or polymerization products from fatty acids, sterols of various nature, cyclic derivatives (e.g. furanoic acids) etc., as well as by several environmental pollutants (such as benzenes, polychlorinated diphenyls and benzofurans, like PCB, DDT etc.), pesticides, mercury derivatives etc., which are all highly toxic or even mutagenic or carcinogenic). In this respect, a purification – but not a concentration – is absolutely compulsory.

However, the concept of fatty acids compositions, in particular DHA, with a high concentration, is so foreign to Nishikawa et al. that they propose the use of other fatty acids as carriers or diluents (see col. 2, lines 64-66: “animal fats and oils, vegetable fats and oils, coconut oil”). If a skilled person had followed the suggestions of Nishikawa et al., he/she would have never tested a composition containing DHA with a concentration not lower than 70% b.w. of the total fatty acids weight in the composition, as presently claimed, and he/she would have reached the conclusion that DHA only displays a very modest activity, as occurred in the electrophysiological *in vitro* test of Nishikawa et al. (example 1 and Fig. 1A-1D), where the effect of a 30 µM concentration of DHA was not substantially higher than that of the 1 µM concentration of its hydroxy and epoxy metabolites.

In stark contrast, the present application describes demonstration, by *in vivo* tests, that the high concentration compositions as presently claimed are endowed with an activity that is by far higher than that of diluted compositions, much more than proportionally to their content. Importantly, regarding the *in vivo* effects found in Nishikawa et al. (example 2), the *in vitro* electrophysiological effects on the NMDA receptors blocked by phencyclidine (example 1) could only demonstrate a mere interference with this receptor system. In the *in vivo* test, a direct clinical test, it was ascertained that a one-month treatment with 3x300 mg DHA brought improvements in schizophrenia negative symptoms in most patients. Nothing more is said, but that neither primary side effects nor significant variations in biochemical blood and urine tests were detected and that a reduced total cholesterol and an increased HDL-cholesterol was found,

although with no significant differences in these values. Therefore, one of skill in the art (contrary to the statement by the Examiner on page 8, first paragraph) would certainly conclude that no improvement of the positive symptoms has been achieved.

Unlike with negative symptoms, positive symptoms include behavior disorders and the inability to think in a coherent manner, associated with abnormal sensations (allucinations) and illusory beliefs (delusions), and are characterized by psychomotor excitation. Applicant's experiments on mice (see, e.g., Example 6 of the present application and the 1.132 Declaration filed herewith) have instead demonstrated that the compositions according to the present invention can counteract the induced schizophreniform psychosis (hyperactivity and excitatory-toxic effects, which are typical of the positive syndrome). The presently claimed method thus provides a treatment of schizophrenia, based on a composition that acts through a mechanism of affinity towards the NMDA receptors, other than the more traditional D2 receptors for dopamine, and is strongly active on the positive symptoms and perfectly tolerated and free of the side effects of all the known anti-psychotic/neuroleptic drugs, such as sedative effects, extrapyramidal effects, including tardive diskynesia, and hypotensive effects, accompanied by several other neurological, metabolic and cardiovascular effects, as well as by frequent blood dyscrasia. Note that claim 30 as amended herein recites schizophrenia showing positive symptoms, and claim 31, as amended herein, specifically recites paranoid schizophrenia.

On page 7 of the Office Action, the Examiner asserts that Nishikawa et al. teaches that an oral antipsychotic comprising DHA or derivatives thereof can be formulated as capsules (see page 7, last paragraph). However, claim 44 of the present application recites that the drug is in the form of soft gelatine capsules; the exemplified formulations are in the form of soft capsules and contain the oily compositions in pure form (apart from the addition of fractions of milligram of tocopherol as antioxidant), instead of the numerous organic and inorganic carriers and diluents in various weight ratios, as disclosed in Nishikawa et al. (see col. 2, line 47 to col. 3, line 25).

Concerning the Examiner's observation that Nishikawa et al. teaches that ethyl esters of DHA can be employed as derivatives, Applicant asserts that Nishikawa et al. is not an enabling reference with respect to use of ethyl esters of DHA, and would not motivate one skilled in the art to use ethyl esters of DHA in a formulation for treating schizophrenia. Ethyl esters of DHA are neither claimed nor mentioned in the examples of Nishikawa et al., whereas the free acid is

used in examples 1 and 2 and the use of hydroxylated metabolites of DHA is claimed in Nishikawa et al. On the contrary, ethyl esters of DHA have been specifically tested in the present application.

Before turning to Horrobin and Chen, Applicant submits that all the scientific works published after the publication of Nishikawa et al. in 1992 have led to the progressive acknowledgement that other omega-3 acids, particularly EPA, were definitely superior in activity with respect to DHA. For example and in particular, Mellor et al. (Human Psychopharm., 1996, listed on the IDS filed July 21, 2006), reported that omega-3 acids, especially EPA, improve the positive symptoms of schizophrenia and tardive dyskinesia, as demonstrated by the administration of fish oil (containing about 18% EPA and 12% DHA). Further, Mellor et al confirmed (see, e.g., the abstract, lines 1-2) that certain n-3 and n-6 EFAs are depleted in cell membranes from red blood cells (RBC) and brains of patients suffering from schizophrenia. It was also therein reported that a greater intake of n-3 fatty acids, especially EPA, was associated with less severe schizophrenic symptoms, in particular positive symptoms, as well as tardive dyskinesia (TD, see, e.g., the abstract, lines 4-6). In fact, supplementation of the diet with 10g/day of concentrated fish oil (i.e. 18% of EPA and 12% of DHA, see Mellor et al., page 40, "Materials") was reported to result in significant amelioration of both schizophrenic symptoms and TD ascribable to the increased level of n-3 fatty acids in RBC membranes (abstract, lines 7-10 and page 41, paragraph bridging the columns). Table 5 of Mellor et al. shows a 274% EPA (20:5 n-3) increase (0.91 to 3.4 mg%) and a 41.8% DHA (22:6 n-3) increase (5.05 to 7.16 mg).

As another example, U.S. Patent No. 6,331,568 to Horrobin (the "568 patent", listed in the IDS filed July 21, 2006), describes the poor activity found in Mellor et al. and demonstrates that the actual active substances, rather than DHA, are EPA and SA (stearidonic acid), because both of them are efficient inhibitors of phospholipase PLA2, while DHA is not. In addition, the '568 patent remarks that the modestly beneficial effects obtained by supplementing a mixture of 18% EPA-12% DHA, as disclosed in Mellor et al., could have been caused by either component or both of them (col. I, line 64 to col. 2, line 3). In order to better understand the activity of n-3 fatty acids, the '568 patent therefore explores treating schizophrenia and TD by administering (col. 2, lines 8-20):

('EPA group') 20 ml of a 40% emulsion providing 8g of an oil containing

2.0 g (25%) of EPA and 0.4 g (5%) of DHA

or

('DHA group') 20 ml of a 40% emulsion providing 8g of an oil containing 2.3g (28.75%) of DHA and 0.5g (6.25%) of EPA

or

placebo,

finding that "the DHA group was not significantly different from placebo, whereas the EPA group was significantly better than both the DHA group and the placebo group" (emphasis added, col. 2, lines 30 - 33). In particular, the author concludes that "there can be no doubt that EPA is primarily responsible for the positive effects" (col 2, lines 37-39), as it is further demonstrated, besides by clinical evidence, also by biochemical arguments, according to which **EPA is a potent inhibitor of phospholipase PLA2, "whereas the relatively similar fatty acid, DHA is not"** (emphasis added, col. 2, lines 48-58).

Further, the '568 patent also discloses that another n-3 fatty acid, SA, "is as effective, in inhibiting PLA2, as is EPA" and that, **unlike DHA**, it can be advantageously effective in treating schizophrenia (col. 2, line 59 to col. 3 , line 4). In other words, the '568 patent *teaches away* from the use of DHA and from the disclosure of Mellor et al. (see col.1, lines 45-51) as to the significance and effectiveness of combining n-6 and n-3 fatty acids, i.e., *teaches away* from the combination of DHA and EPA, **shifting indeed the attention of the person skilled in the art to EPA and SA (both n-3 acids)**, which are only optionally combined with n-6 EFAs (see, e.g., claim 1 of the '568 patent). A claimed combination of prior art elements may be nonobvious where the prior art teaches away from the claimed combination and the combination yields more than predictable results.¹

As another example, in U.S. Patent No. 6,384,077 to Peet (the " '077 patent", listed on the IDS filed July 21, 2006), this reference confirms the hypotheses of Horrobin in the '568 patent about the activity of EPA, if this substance is substantially pure and substantially free of DHA (col. 1, lines 54-63). In particular, the person skilled in the art is taught to treat psychiatric disorders by using pure or nearly pure EPA and its derivatives (col. 3, lines 14-19) based on the

¹ Crocs, Inc. v. U.S. Int'l Trade Comm'n., 598 F.3d 1294 (Fed. Cir. 2010), cited in the USPTO's recently updated examination guidelines on obviousness, see <http://edocket.access.gpo.gov/2010/pdf/2010-21646.pdf>

observation that the common pathological basis for the major psychotic mental illnesses – i.e. schizophrenia, bipolar disorder and major depression- and for many neurodegenerative disorders as well, can be identified with the hyperactivity of phospholipase PLA2 (col. 3, lines 20-32 and col. 4, lines 8-18), following the teachings of the ‘568 patent also for this aspect. The teachings of the ‘077 patent confirm that such hyperactivity can be effectively inhibited by highly purified EPA and that other fatty acids, among which DHA, compete with EPA, i.e. other PUFAs are detrimental to the activity of EPA (col. 6, lines 23-31), as clinically shown by comparing two preparations (25% EPA + 8% DHA - 96% EPA + DHA <3%: col. 6, lines 38-55). The ‘077 patent, however, discloses that the activity of substantially pure EPA must be carried out “*in conjunction with a drug which acts primarily on neurotransmitter metabolism or receptors*” (see e.g. claim 1 of the ‘077 patent).

In summary, all the scientific works published after 1992 would have led the skilled person towards selecting EPA for treating psychiatric and degenerative disturbances of CNS by discouraging the use of other PUFAs and, in particular, representing a substantially uniform consensus to *opposing* the use of DHA (as presently claimed).

Regarding the teachings of Horrobin, this reference discloses that the presence of an n-6 acid in a composition for treating schizophrenia is necessary, due to a deficiency in the red cell membranes of schizophrenic patients. It is to be noted, however, that Horrobin himself in a later-filed patent (the ‘586 patent) declares that, after clinical verification, DHA was found to be substantially inactive and not significantly different from the placebo, whereas EPA was strongly active. The conclusion drawn in the ‘568 patent (see e.g., claim 1) that the true active substances are EPA or stearidonic acid, renders the teachings of Horrobin (U.S. Patent No. 4,977,187) insignificant such that one skilled in the art would not combine them with those of Nishikawa et al. and Chen to conceive of the presently claimed method.

Applicant asserts that the possibility to use vitamin E (or not) is devoid of any significance, because the usual low doses (e.g. 0.3 or 3%) have only the function of stabilizing compositions and formulations *in vitro*, whereas only substantially higher doses, e.g. >10% may have significance *in vivo*, in both cases with a poor correlation with the activity on schizophrenia. Support for this statement can be found in Applicant’s EP application no. EP 0 699437 (listed on the IDS filed July 21, 2006 - see Table 1, Claim 1) which describes

experimental verification that only substantially higher doses, e.g. >10% may have significance *in vivo*, in both cases with a poor correlation with the activity on schizophrenia. There is thus a sharp contrast between the teachings of the present application and those of Horrobin: according to Horrobin, the true active substance is EPA (DHA being totally inactive), optionally admixed to n-6 acids, while, according to the present application, the active substance is DHA, in particular at a high concentration (and thus substantially free of n-6 acids); EPA is accepted within certain limits, as it provides some side advantages, without impairing the safety and tolerability of the formulation. The results of the presently claimed invention were unexpected in view of the prior art and the conventional wisdom at the time the application was filed². Applicant's experimental results described in Example 6 of the application, and in the 1.132 Declaration filed herewith, show that the presently claimed method alleviates symptoms of Schizophrenia in mammals. These results are unexpected, since the prior art teaches away from the claimed combination of DHA and EPA, and because the prior art teaches that GLA is an essential feature of a composition for treating Schizophrenia, yet the presently claimed method that alleviates Schizophrenia symptoms in mammals involves a composition that does not include GLA.

Turning now to Chen et al., this document was cited because it teaches that schizophrenia encompasses paranoid, disorganized, catatonic and undifferentiated schizophrenia. The substances described in Chen et al. are completely unrelated to the presently claimed active substances. Applicant asserts that this reference fails to cure any of the deficiencies of Nishikawa et al. or Horrobin.

As for the combination of Horrobin, Nishikawa et al. and Chen, and the Examiner's conclusion that it would have been obvious to combine components that were individually known for the treatment of schizophrenia, such as DHA, EPA, and GLA, to obtain a combination, which is in turn active, Applicant submits that the claimed combination of references does not render the presently claimed invention obvious. Firstly, Applicant disagrees with the assertion that DHA and EPA are known agents for the treatment of schizophrenia, for the reasons given above. Secondly, there is nothing in any of the cited references that explicitly or implicitly suggest modifying their teachings to result in the presently claimed invention. With

² Crocs, Inc. v. U.S. Int'l Trade Comm'n., *supra*

regard to DHA as described above, all the scientific works published after 1992 would have led the skilled person away from using DHA, representing a substantially uniform consensus to opposing the use of DHA (as presently claimed). See, e.g., Mellor et al., the '568 patent, and the '077 patent. In particular, Mellor et al. discloses an activity of EPA (18%) and DHA (12%) at low concentration on the positive symptoms of schizophrenia and on tardive dyskinesia, but Applicant's data described in the 1.132 Declaration filed herewith disproves the accuracy of the Mellor et al. disclosure. Both the '568, and '077 patents teach that the active substance is EPA and state that DHA is inactive and even antagonistic towards EPA, and this represents the most recent and most appropriate prior art to the present application.

With regard to EPA and GLA, Horrobin (U.S. Patent No. 4,977,187) discloses that the presence of GLA (which is an omega-6 acid) is an essential feature, because the phospholipids of red cells in schizophrenic patients are deficient in both omega-3 and omega-6 acids. Thus, the absence of GLA from the presently claimed composition is unexpected and non-obvious. Moreover, the inventor of US 4,977,187 himself, i.e., Horrobin, in his later-filed '568 patent, when declaring that EPA is the true active substance, based on both clinical and biochemical experimentation, gives a clear indication *against* the use of EPA in combination with DHA, which is totally inactive (this statement is then wholly confirmed by the teachings of the '077 patent). Contrary to the Examiner's assertion on page 9, lines 16 to 21, regarding soft gelatin capsules, formulation in soft gelatine capsules is not obvious, because neither Nishikawa et al. nor Horrobin disclose or even suggest soft gelatine capsules. Applicant asserts that because the presently claimed composition including use of a combination of DHA and EPA for treating schizophrenia is not obvious for the reasons given above, the ratio set forth in claims 29 and 34 is also not obvious over the prior art, and that the presently claimed doses are not superimposable to those of the prior art.

It is clear that the prior art *teaches away* from using DHA alone, and to use instead EPA, but not in association with DHA. Applicant is aware that when rejecting a claim based on a motivation to combine, an explicit suggestion to combine the prior art is not necessary, and that the motivation to combine may be implicit and may be found in the knowledge of one of ordinary skill in the art. However, in the instant combination of references, one of ordinary skill in the art would find no motivation, implicit or explicit, to alter the methods of Nishikawa et al.,

based on Horrobin's disclosure that an n-6 acid is necessary in a composition for treating schizophrenia, and Chen's disclosure of different types of schizophrenia. In view of the prior art's *teaching away* and the conventional wisdom at the time the invention was made, the presently claimed invention is non-obvious and inventive over the prior art.

Based on the foregoing, Applicant submits that the combination of Nishikawa et al., Horrobin, and Chen does not render the present invention obvious within the meaning of 35 U.S.C. 103. Each reference fails to implicitly or explicitly suggest modifying its teachings to arrive at Applicant's invention, the prior art actually *teaches away* from the claimed invention, and the results of the presently claimed invention were unexpected in view of the prior art.

Accordingly, withdrawal of this rejection is respectfully requested.

Conclusion

The currently pending claims before the Examiner are supported throughout the specification and patentable over the prior art. No new matter has been added. This application is now in full condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge the \$130.00 fee for a retroactive one month extension of time to the attached credit card authorization. Although no additional fees are believed due, the Commissioner is hereby authorized to charge any deficiency or credit any surplus to Deposit Account No. 14-1437.

The Examiner is cordially invited to call the undersigned if clarification is needed on any matter within this amendment, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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